Conferences and Reviews

Atherosclerosis—Reversal With Therapy

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Evidence for atherosclerosis reversal comes from studies in animals wherein atherosclerosis is induced and then allowed to regress, autopsy studies of starved humans, and angiographic studies testing antiatherosclerosis treatment. Animal models and autopsy studies have provided detailed histologic and biochemical descriptions of regression. Cellular and subcellular information exists on what can occur, but because the same lesions are not reexamined, what actually does occur is unknown.

Studies of isolated arterial cell systems and intact lesions indicate that atherogenesis involves at least the following: Increased permeability of the endothelium to macromolecules such as low-density lipoprotein; platelet adherence to areas of functional endothelial injury or denudation; the entrance of monocytes or macrophages and lymphocytes into the subintimal space; and the secretion of growth factors by platelets, injured endothelium, and macrophages. These processes can be initiated or enhanced by various vasoactive agents that induce endothelial cell constriction with the opening of endothelial junctions. These processes also can recruit smooth muscle cells from the media to the subintima where they proliferate. Proliferating smooth muscle cells, along with macrophages, can internalize lipids and lipoproteins to form foam cells. Subintimal smooth muscle cells can also synthesize collagen, elastin, glycosaminoglycans, and other connective tissue elements that trap lipoproteins. Peroxidative injury increases the atherogenic potential of both cholesteryl ester-rich (low-density) and triglyceride-rich (very-low-density and intermediate-density) lipoproteins. Steep oxygen gradients within the arterial wall create local conditions for free radical generation, and any increase in residence time of lipoprotein particles can be atherogenic. In summary, there are many areas where treatment may retard or reverse atherogenesis.

Angiographic trials that identify and track individual human lesions have shown that reducing known atherogenic risk factors can lessen coronary and femoral atherosclerosis. But they provide no information on events within arterial wall cells or the intracellular matrix. They deal only with lesions that intrude into the vessel lumen and obtain measurements at infrequent intervals. The weight of evidence is that regression is possible, but there is no consensus on the most effective therapy. The challenge for future trials is to select optimal targets for intervention among the known atherogenic processes.

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In 1967 Ost and Stenson treated 31 patients with atherosclerosis with regimens of 3 to 6 grams of nicotinic acid a day. Three showed improvement on femoral angiograms after a treatment period of three years, accompanied by an increase in pulse volume and improved walking capacity. The lipid levels achieved by niacin therapy were not reported, but it is probable that they were reduced.[1]

Eight patients with familial hypercholesterolemia were treated by Thompson and co-workers with repeated plasma exchange, and three showed measurable improvement in coronary artery and supravalvular aortic lesions.[2]

Barndt and colleagues reported treating 25 patients with hyperlipidemia with diet, lipid-lowering medication (primarily clofibrate and neomycin), and antihypertensive medication (if indicated).[3] Nine showed regression in femoral atherosclerosis (primarily early lesions) after 13 months. Patients showing regression were those with a substantial reduction in blood total cholesterol levels from 8.05 to 6.35 mmol per liter (311 to 246 mg per dl), triglycerides from 4.08 to 1.63 mmol per liter (362 to 143 mg per dl), and systolic and diastolic blood pressure levels from 132 to 123 mm of mercury and 85 to 79 mm of mercury, respectively. Patients showing progression did not have notable reductions in these risk factors.

Kuo and associates reported that treatment with combined colestipol and niacin therapy could stabilize atherosclerotic coronary artery lesions for periods as long as

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ABBREVIATIONS USED IN TEXT

CLAS = Cholesterol Lowering Atherosclerosis Study
HDL = high-density lipoprotein
LDL = low-density lipoprotein
NHLBI = National Heart, Lung and Blood Institute

seven and a half years. This evidence was based on serial coronary angiographic examinations in 25 patients.[4]

3 Influential Early Trials

Femoral Artery Trial With Selective Lipid-Lowering Therapy

Duffield and co-workers conducted an unblinded but randomized trial in which 24 patients (average age, 56 years) with advanced femoral atherosclerosis were treated with lipid-lowering drugs assigned according to their Fredrickson phenotype.[5] Entry criteria were claudication of six months' duration and plasma cholesterol levels of more than 6.47 mmol per liter (250 mg per dl). Patients with diabetes mellitus, diastolic hypertension, and rest pain were excluded. There were 12 drug-treated subjects (8 with type II, 3 with type III, and 1 with type IV hyperlipidemia) and 12 "usual care" patients whose lipid levels were untreated (8 with type II, 1 with type III, and 3 with type IV). Patients with type II hyperlipidemia were treated with a regimen of 12 to 24 grams of cholestyramine resin a day plus 3 to 6 grams of niacin. Patients with type IV hyperlipidemia were treated with niacin; those with type III were given clofibrate. Diet in both groups included 30% of calories as fat with a polyunsaturated to saturated fat ratio of 1 and a cholesterol intake of less than 250 mg per day.

Angiograms were repeated after a mean period of 19 months. In the interval between angiograms, total blood cholesterol levels averaged 6.03 mmol per liter (233 mg per dl) in treated patients versus 7.43 mmol per liter (287 mg per dl) in patients receiving usual care, triglycerides 1.86 mmol per liter (163 mg per dl) in treated versus 2.96 mmol per liter (260 mg per dl) in patients receiving usual care, high-density lipoprotein (HDL) cholesterol 1.54 mmol per liter (59.6 mg per dl) in treated patients versus 1.09 mmol per liter (42.3 mg per dl) in those receiving usual care, and LDL cholesterol 3.88 mmol per liter (150 mg per dl) in treated patients versus 5.10 mmol per liter (197 mg per dl) in those receiving usual care. Among 144 femoral segments in treated patients, 10 showed progression; among 156 segments in the usual-care group, 27 showed progression, a difference significant at the .01 level. This study is noteworthy despite the small number of subjects (too few for a formal per-patient test of treatment effects). It demonstrated that lipid-lowering therapy selected according to the lipid transport pattern can retard advanced femoral atherosclerotic lesions.

Pioneering Coronary Artery Trial

The National Heart, Lung and Blood Institute (NHLBI) Type II Study was a randomized, placebo-controlled, double-blind coronary angiographic study.[6] It tested the use of 24 grams per day of cholestyramine in subjects with type II hyperlipoproteinemia and overt coronary artery disease, excluding those with 75% or more stenosis of the left main coronary artery. A criterion for entry was LDL-cholesterol levels above the 10th percentile of the general population after a month of a low-cholesterol low-fat diet. Average entry levels were as follows: total cholesterol, 8.36 mmol per liter (323 mg per dl); triglyceride, 1.87 mmol per liter (164 mg per dl); HDL cholesterol, 1.01 mmol per liter (39 mg per dl); and LDL cholesterol, 6.50 mmol per liter (251 mg per dl); the two trial groups were evenly matched. The average entry blood pressure was 122/79 mm of mercury, 43% of subjects smoked, 26% of subjects were sedentary, and again the two trial groups were matched. A low-fat diet reduced LDL-cholesterol levels 5% in both groups. During drug treatment, LDL-cholesterol levels in the placebo group were reduced an additional 5% and LDL-cholesterol levels in the cholestyramine group were reduced 26%. Triglyceride levels in both groups were increased 25%.

The original study design called for 250 patients randomly assigned to two treatment arms, but recruitment was stopped after 54 months when 143 patients had been randomly allocated. In all, 57 patients in the placebo group and 59 cholestyramine-treated subjects had second angiograms after five years. Angiograms were evaluated by human panelists with the temporal sequence and treatment masked. Results from three separate panels of three angiographers were combined for the final analysis. On average, the panelists evaluated 5.4 lesions per subject. After the blind was broken, subjects were classified as having definite progression, probable progression, definite regression, probable regression, mixed response, and no change.

Trial results were as follows: significant per-subject differences between drug and placebo use were not detected; cholestyramine use significantly retarded progression in lesions with 50% or greater stenosis ($P < .05$); and an increased ratio of HDL to LDL cholesterol predicted lesion stabilization. In 1989, 54 film pairs from the study were reevaluated by the quantitative procedure of Brown and associates.[7] This confirmed the occurrence of mixed lesion response and indicated that the initial severity of stenosis correlated strongly with new total occlusion and with disease progression. The influence of the NHLBI Type II trial on later studies has been substantial because it led later investigators to test the use of more aggressive lipid-lowering therapy (drug-induced changes in total and LDL-cholesterol levels were not large, and triglyceride levels increased); it demonstrated that both progression and regression of lesions could occur in the same subject; it indicated that lesion severity at baseline influenced treatment response, with more severe lesions showing greatest benefit; and it introduced the use of human panel reading for evaluating films.

First Coronary Angiographic Trial Testing Diet

The Leiden Intervention Trial, which was started in 1978 and completed in 1981, recruited 61 patients with

stable angina and one or more lesions exceeding 50% stenosis who were not candidates for coronary artery bypass grafting.[8] The trial was not randomized or blinded; however, coronary angiograms were evaluated by readers who did not know blood lipid levels or the order of examination. All patients were assigned to a vegetarian diet that reduced saturated fat and cholesterol intake while increasing the intake of polyunsaturated fat. It was estimated that the diet at entry provided 11% of calories from saturated fat and 8.5% from unsaturated fat and that daily cholesterol intake was 88 mg per 1,000 calories. After a year, diet estimates indicated that 6.6% of calories were from saturated fat, 16.8% from polyunsaturated fat, and daily cholesterol intake was 30 mg per 1,000 calories.

Of 53 who started the diet, 4 died in the first year (3 with myocardial infarction, and 1 suddenly) and 7 patients had coronary artery bypass grafting. Angiography was not repeated in three patients (because of a malignant tumor in 2 and refusal in 1). Studies were repeated in 39 patients, and films were evaluated both by visual inspection and computer analysis.[8] Of the 39 patients, 21 showed progression. Among the 18 without progression, total cholesterol reduction was 9%. Lesion progression was strongly related to the total cholesterol:HDL-cholesterol ratio, and no coronary lesion progression occurred in patients with a total cholesterol:HDL-cholesterol ratio of less than 6.9 throughout the study or in those who had reduced a high ratio at baseline to less than 6.9. The most important finding of the Leiden study was the suggestion that lesion progression can be arrested by dietary modification without weight loss. Before this report, the literature on atherosclerosis regression in humans was limited to autopsy studies in starved populations.[9]

There were other noteworthy aspects of the Leiden Intervention Trial: The first parallel use of human visual reading and fully automated computer lesion measurement showed agreement in the classification of subjects with a stable lesion versus those with progression; as in the NHLBI Type II Study, lesion status at baseline was shown to influence treatment effect, with the greatest benefit to lesions greater than 50% stenosis; and the first within-group analysis (in this case because there was no control group) was useful in ranking the magnitude of risk factor effects.

6 Recent Coronary Angiographic Trials

Cholesterol Lowering Atherosclerosis Study

In the first angiographic trial in which clear evidence of atherosclerosis regression was demonstrated, combined therapy with colestipol and niacin was tested.[10] A pretrial of drug therapy was used to identify subjects with responsive lipid levels. The Cholesterol Lowering Atherosclerosis Study (CLAS) randomly allocated 188 nonsmoking men with previous coronary artery bypass grafts; 162 subjects had two-year angiograms, and 103 had four-year angiograms. Colestipol-niacin treatment produced large decreases in total cholesterol levels from 6.37 to 4.65 mmol per liter (246 to 180 mg per dl), total triglycerides from 1.72 to 1.25 mmol per liter (151 to 110 mg per dl), and LDL cholesterol from 4.43 to 2.51 mmol per liter (171 to 97 mg per dl). Drug treatment increased HDL-cholesterol levels from 1.15 to 1.57 mmol per liter (44.6 to 60.8 mg per dl). Coronary angiograms from the study have been evaluated by both human panel readers[10] by modification of the method used in the NHLBI Type II Study and by fully automated quantitative coronary angiography.[11] The two methods measure somewhat different but overlapping lesion populations, with panel readers addressing more severe lesions,[12] but they agree on treatment effects. Drug treatment produced a significant reduction in the number of native artery lesions that progressed ($P < .03$) and the percentage of patients with new lesion formation ($P < .04$). Drug treatment also produced a significant reduction in the number of patients with new lesion formation ($P < .04$) and other adverse changes ($P < .03$) in the bypass grafts. At two years, regression was found in 16.2% of the drug-treated group compared with 3.6% of the placebo-treated group ($P < .01$). The evidence for benefit retained strong statistical significance after the cohort was divided at the midpoint for an entry cholesterol level of 6.24 mmol per liter (241 mg per dl).

In all, 103 subjects remained on their assigned treatment with blinding maintained for a total of four years and had a third angiogram.[13] Changes in the levels of blood lipids, lipoprotein cholesterol, and apolipoproteins were maintained, and at four years significantly more drug-treated subjects showed nonprogression (52% drug group versus 15% placebo group, $P << .01$) and regression (18% drug group versus 6% placebo group, $P = .04$) in native coronary artery lesions. Significantly fewer drug-treated subjects had new lesions develop in native coronary arteries (14% drug group versus 40% placebo group, $P < .001$) and bypass grafts (16% drug group versus 38% placebo group, $P < .001$). Again, the evidence for benefit retained strong statistical significance after the cohort was divided at the midpoint for an entry cholesterol level of 6.24 mmol per liter (241 mg per dl).

A within-group analysis of diet records in CLAS subjects in the placebo group showed that dietary changes that reduced blood cholesterol levels could reduce the incidence of the formation of new coronary artery lesions.[14] The baseline diet of the entire placebo group had a total fat content that averaged 32% of total calories and a daily cholesterol intake of 258 mg. A total of 64 men, in whom new lesions did not develop during the first two study years, made dietary changes that reduced total plasma cholesterol levels from 6.29 to 5.95 mmol per liter (243 to 230 mg per dl). They significantly reduced dietary total fat, saturated fat, monounsaturated fat, and cholesterol and increased polyunsaturated fat. The major steps to accomplish this were the substitution of low-fat meat and dairy products for high-fat meat and dairy products. Another 18 men in whom new lesions developed did not reduce their cholesterol level from a baseline level of 6.24 mmol per liter. They made no notable dietary changes except to increase their polyunsaturated fat intake.

Subjects in CLAS also had femoral angiograms.[15] The two-year treatment effect on femoral atherosclerosis in

this study was considerable but was less pronounced than the benefit observed in coronary arteries and aortocoronary bypass grafts. The annual change rate in computer-estimated atherosclerosis, a measure of lumen abnormality, was evaluated between treatment groups.[16] A significant per-segment treatment effect was found in segments with moderately severe atherosclerosis ($P < .04$) and in proximal segments ($P < .02$). When segmental measures of computer-estimated atherosclerosis were combined into a per-patient score using an adaptation of the coronary scoring procedure used in the NHLBI Type II Study, a significant treatment effect was observed ($P < .02$).[15]

A pilot study of carotid ultrasound imaging was included in CLAS.[17] In all, 78 subjects (39 drug- and 39 placebo-treated) had ultrasound studies at baseline and two and four years. Computer images were processed to measure common carotid far-wall thickness. Computer operators were blind to the treatment group. The carotid intima-media thickness measured by ultrasonogram was correlated at baseline with visually read angiographic stenosis and at two years with a robust computer measure of carotid atherosclerosis. Drug-treated subjects showed substantial progressive reduction in carotid thickness at two and four years. Placebo-treated subjects showed significantly increased wall thickness at two and four years with differences in the change in thickness between the two groups significant at both times ($P << .01$). Reduced levels of apolipoprotein B and increased levels of HDL cholesterol and HDL-associated apolipoprotein C-III were significant predictors of carotid wall thinning. These findings indicate that carotid atherosclerosis at a stage before lesions intrude into the vessel lumen can be reduced by colestipol-niacin treatment. They also indicate the feasibility of image-processed carotid ultrasonographic trials of two years' duration and include 50 subjects per treatment arm to test early atherosclerosis treatment.

Program on the Surgical Control of the Hyperlipidemias

The largest trial reported to date tested lipid lowering by the partial ileal bypass operation.[18] The principal end points were coronary angiographic and clinical findings, total mortality, and morbidity or mortality due to coronary heart disease. The study population consisted of 838 patients who had survived a first myocardial infarction 6 to 60 months before being randomly allocated for the control (n = 417) or surgery (n = 421) group. The average age was 51 years, and 90.7% were men. Eligible subjects were required to have a total plasma cholesterol level of at least 5.69 mmol per liter (220 mg per dl) or an LDL-cholesterol level of at least 3.62 mmol per liter (140 mg per dl) if their total plasma cholesterol level was between 5.18 and 5.67 mmol per liter (200 and 219 mg per dl) on a phase II diet for six weeks. Major exclusion criteria were hypertension of greater than 180/105 mm of mercury, body weight 40% above ideal, diabetes mellitus, previous cardiac operation, pacemaker implantation, and left main coronary artery stenosis of greater than 75%.

The mean follow-up period was 9.7 years. The primary end point of the trial was death due to any cause. Secondary end points were cause-specific death (determined through a blinded review by an external committee) and recurrent confirmed or suspected myocardial infarction. Additional secondary end points were nonfatal myocardial infarction with electrocardiographic and cardiac enzyme changes, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, cardiac transplantation, and peripheral vascular operation.

When compared with the control group at five years, the surgery group had a total plasma cholesterol level 23.3% lower (4.71 versus 6.13 mmol per liter [182 versus 237 mg per dl], $P << .01$); an LDL-cholesterol level 37.7% lower (2.66 versus 4.30 mmol per liter [103 versus 166 mg per dl], $P << .01$); and an HDL-cholesterol level 4.3% higher (1.06 versus 1.04 mmol per liter [41.0 versus 40.2 mg per dl], $P = .02$). The most common side effect of the partial ileal bypass procedure was diarrhea. Other more serious side effects were kidney stones, gallstones, and intestinal obstruction.

Overall morbidity and mortality due to coronary heart disease were not significantly reduced, but the rate of death due to coronary heart disease and confirmed nonfatal myocardial infarction combined was 35% lower in the surgery group (125 versus 82 events, $P < .001$). Overall mortality in the surgery subgroup with an ejection fraction of greater than or equal to 0.50 was 36% lower (control versus surgery, 0.39 versus 0.24, $P = .02$). During follow-up, 137 control-group and 52 surgery-group patients underwent coronary artery bypass grafting ($P << .01$).

A comparison of baseline coronary arteriograms with those obtained at three, five, seven, and ten years consistently showed less disease progression in the surgery group ($P < .001$). This study is important because there is a prolonged follow-up with a sustained reduction of blood lipid levels, and improvement in coronary angiographic anatomy has been shown to result in reduced cardiac mortality and morbidity. This study remains a landmark, although the role of partial ileal bypass as a procedure for the management of hypercholesterolemia has been greatly reduced by the effectiveness of current lipid-lowering drugs.

Familial Atherosclerosis Treatment Study

The Familial Atherosclerosis Treatment Study was a three-arm trial (colestipol-niacin, colestipol-lovastatin, and conventional treatment) conducted in subjects with hyperlipoproteinemia that also showed that improved coronary angiographic anatomy is associated with reduced cardiac morbidity.[19] A total of 146 men 62 years of age or younger, with elevated apolipoprotein B levels and a family history of coronary artery disease, were randomly assigned to one of three therapeutic strategies. All patients had evidence of coronary atherosclerosis on a baseline arteriogram, with at least one vessel showing 50% stenosis or three showing 30% stenosis.

In the niacin-colestipol-treated group (average age 47

years, 22% smokers, and 44% with a history of hypertension), the colestipol therapy was begun at a dose of 5 grams, three times a day with meals, and increased to 10 grams, three times a day after ten days. Metamucil and dietary bran were used to control constipation. Niacin therapy was started at 125 mg twice a day and gradually increased to 500 mg four times a day (with meals and at bedtime) at one month and 1 gram four times a day at two months. If the LDL-cholesterol level did not fall below 3.10 mmol per liter (120 mg per dl) after three months, the dose of niacin was increased to 1.5 grams (3 tablets) four times a day, but no further.

In the lovastatin-colestipol-treated group (average age 48 years, 23% smokers, and 34% with a history of hypertension), lovastatin therapy was begun at a dose of 20 mg twice a day (in the morning and at bedtime). If the LDL-cholesterol level did not fall below 3.10 mmol per liter after three months, the dose of lovastatin was increased to 40 mg twice a day.

In the conventional therapy group (average age 47 years, 26% smokers, and 28% with a history of hypertension), patients received placebos for colestipol and lovastatin. For purposes of blinding, the lovastatin placebo dose for a patient assigned to conventional therapy was doubled each time the lovastatin dose was doubled for a patient assigned to receive lovastatin and colestipol. If baseline LDL-cholesterol levels exceeded the 90th percentile for their age (43% of the group), patients on conventional therapy received colestipol instead of its placebo.

In matched coronary angiograms at baseline and 2.5 years later, the borders of each lesion and the catheter were manually traced from selected frames onto a standard form. For lesions classified previously by visual inspection as unchanged or definitely changed, two selected frames were traced for each view. For "possibly changed" lesions, three frames were traced for each view, each by two technicians. All tracings were reviewed for accuracy by an experienced technician and were then digitized and processed. The diameter of the lumen at the point of greatest local narrowing (minimum diameter) and nearby normal diameters were measured, in millimeters, with the catheter used as a scaling factor. The two principal measures of disease were the minimum diameter and the percentage of stenosis:

$$\% \text{ Stenosis} = 100\,(1 - \text{DM/DN}),$$

where DM denotes the minimum diameter and DN normal diameter. Each estimate was an average of the estimates for the tracings measured, which averaged 3.1 per film (range, 2 to 12).

In the conventional therapy group, 46% of the patients had definite lesion progression (and no regression) in at least one of nine proximal coronary artery segments; regression was the only change in 11%. By comparison, progression (as the only change) was less frequent among patients who received lovastatin-colestipol (21%) and those who received niacin-colestipol (25%), and regression was more frequent (lovastatin-colestipol group, 32%; niacin-colestipol group, 39%; $P < .005$). When lesions were stratified by baseline severity, those with 50% or greater stenosis showed average regression, those with less than 50% stenosis showed only a reduction in average progression. Multivariate analysis indicated that a reduction in the level of apolipoprotein B (or LDL cholesterol) and in systolic blood pressure and an increase in HDL-cholesterol levels correlated independently with the regression of coronary artery lesions.

Clinical events of death, myocardial infarction, or revascularization for worsening symptoms occurred in 10 of 52 patients assigned to conventional therapy as compared with 3 of 46 assigned to receive lovastatin and colestipol and 2 of 48 assigned to receive niacin and colestipol (relative risk of an event during lipid-lowering treatment, 0.27; 95% confidence interval, 0.10 to 0.77).

University of California, San Francisco, Specialized Center of Research Intervention Trial

Subjects in the University of California, San Francisco, Specialized Center of Research Intervention Trial were between 19 and 72 years old and had clinical features of heterozygous familial hypercholesterolemia, such as tendon xanthomas and LDL-cholesterol levels above 5.18 mmol per liter (200 mg per dl) with total triglyceride levels below 7.12 mmol per liter (275 mg per dl) while on restricted dietary saturated fat and cholesterol.[20] Patients without tendon xanthomas were included if they had an LDL-cholesterol level above 6.47 mmol per liter (250 mg per dl) or an LDL-cholesterol level of greater than 5.18 mmol per liter (200 mg per dl) and a first-degree relative with tendon xanthomas. Patients with previous angioplasty, coronary bypass grafting, or multiple infarcts were excluded, as were patients with systemic diseases other than atherosclerosis or hypertension.

Subjects were randomly assigned by sex and age to test and control groups. Both groups received dietary counseling. The test group received aggressive drug therapy to reduce LDL levels with combinations of lipid-lowering agents. These patients were initially given as much as 30 grams of colestipol and as much as 7.5 grams of niacin daily, as tolerated. Of the 40 patients in the treatment group, 36 took niacin, 25 of whom consistently took more than 1.5 grams daily. In addition, 28 patients took 30 grams and 4 took 15 grams of colestipol daily throughout the study. When lovastatin became available as an investigational drug, it was given also; 16 patients took 40 to 60 mg of lovastatin daily in dual- or triple-drug combinations. At the start, the control group was treated with diet alone. Later this group was offered 15 grams per day of bile acid-binding resin. Fourteen patients elected to take colestipol. Seven men took it for an average of 19 months and seven women for an average of 20 months. The control group included those treated with diet alone and those treated with diet plus resin.

Coronary angiography was repeated after two treatment years. The primary outcome variable was a change in the cross-sectional percentage area of stenosis, averaged for all lesions in each subject. All other quantifiable

lesions were analyzed. The mean change in percentage of area of stenosis among controls was +0.80%, indicating progression, whereas the mean change for the treatment group was −1.53%, indicating regression ($P = .04$ by 2-tailed t test for the difference between groups). The effect of the baseline lesion status on the treatment response was not analyzed. Regression among women, analyzed separately, was also significant. When analyzed separately, women in this study showed more lesion benefit to therapy than did men. The change in the percentage of area of stenosis was correlated with LDL-cholesterol levels on the trial.

This trial is important because it demonstrates that regression can occur in women with a substantially greater change in lesions than that observed in men, and it extends information on regression to asymptomatic persons with hyperlipoproteinemia (92% were asymptomatic).

Life-style Heart Trial

The Life-style Heart Trial tested a comprehensive risk reduction program that included a low-fat vegetarian diet, smoking cessation, stress management, moderate aerobic exercise, and group support.[21] The treatment group diet allowed no animal products except egg white and one cup per day of nonfat milk or yogurt containing approximately 10% of calories as fat and 5 mg per day or less of cholesterol. Twice-a-week group discussions led by a clinical psychologist provided social support including stress management training. Subjects were asked to exercise for three hours per week and to maintain target heart rates for 30 minutes of each exercise session.

In all, 22 subjects in the life-style-change group were compared with 19 subjects randomly assigned to a usual-care control group who were not asked to make life-style changes. Patients having angiograms for clinical reasons unrelated to the study were screened, and among 96 eligible patients, 53 were randomly assigned to the experimental group and 43 to the control group. Major entry criteria were patients aged 35 to 75 years of either sex and having measurable coronary atherosclerosis in a nondilated or nonbypassed coronary artery. Left ventricular ejection fractions of greater than 0.25 were required. Randomization was accepted by 28 in the treatment group and 20 in the control group. Control group patients had higher entry total, LDL- and HDL-cholesterol, and triglyceride levels: 6.34, 4.32, 1.35, and 2.45 mmol per liter, respectively (245, 167, 52, and 217 mg per dl), than treatment group subjects, but differences at baseline between the randomized groups were not statistically significant.

Treatment group subjects made substantial life-style changes. The average exercise time was increased from 11 minutes per day to 38. Dietary fat and cholesterol that averaged 31% of calories and 213 mg per day, respectively, on entry were reduced to 7% of calories and 13 mg per day, respectively. The average weight on entry of 92.5 kg (204 lb) was reduced to 82.1 kg (181 lb), and the average blood pressure was reduced from 134/83 to 127/79 mm of mercury. The average total cholesterol, LDL-cholesterol, and apolipoprotein B levels at entry of 5.88 mmol per liter (227 mg per dl), 3.92 mmol per liter (152 mg per dl), and 104 mg per dl, respectively, were reduced to 4.45 mmol per liter (172 mg per dl), 2.46 mmol per liter (95 mg per dl), and 79 mg per dl, respectively. Triglyceride levels, however, increased from 2.38 mmol per dl (211 mg per dl) at entry to 2.91 mmol per liter (258 mg per dl) on trial, and HDL-cholesterol levels remained unchanged.

Follow-up angiographic data were not available for one control and six treated subjects. The control subject underwent emergency angiography, with films unsuitable for analysis. One subject in the experimental group died while exercising. One person in the intervention group who had alcoholism dropped out, and four intervention subjects' films were unavailable or unsuitable for technical reasons.

In the available films, 105 coronary artery lesions in the experimental group were compared with 90 in the control group. For the film analysis, computerized quantitative coronary angiography was done at the University of Texas at Houston. End-point analysis was based on the average lesion change; statistical tests of intervention effects on per-subject scores were not reported. The average percentage of diameter stenosed was reduced from 40.0% to 37.8% in the experimental group and increased from 42.7% to 46.1% in the control group, a differential change of 5.6% ($P = .001$). Larger treatment benefit was found in lesions of greater than 50% stenosis at baseline where the differential effect was 8.6% ($P = .03$). All five women in the study (four in the control group) showed evidence of lesion regression. All were postmenopausal, and none were taking estrogens. A per-subject score was constructed from the sign of the average of lesion change scores and found to be indicative of regression in 18 treatment group subjects with 4 in the treatment group showing progression. Among 19 control group subjects, 8 showed regression, 10 progression, and 1 no change.

This trial is the first randomized study reporting regression without drug or surgical therapy to lower blood lipid level. The sustained reduction of LDL-cholesterol levels with life-style change only is remarkable. It supports the findings from the University of California, San Francisco, trial that indicate that women may be better candidates for lesion regression than are men. It also supports the finding in other studies that lesions of greater than 50% stenosis are more likely to respond to treatment.

St Thomas' Atherosclerosis Regression Study

The St Thomas' Atherosclerosis Regression Trial was a three-arm trial assessing the effects of diet and diet plus cholestyramine in reducing plasma cholesterol levels.[22] It was a randomized, controlled end-point-blinded trial. A total of 90 men with coronary heart disease (angina or past myocardial infarction) who had a mean plasma cholesterol level of 7.22 mmol per liter ± 0.76 (SD) (279 mg per dl ± 29.7) were randomly allocated to receive usual care, dietary intervention, or diet plus cholestyramine. Coronary angiography with fully automated quantitative image analysis was repeated after 39 ± 3.5 months in 74

subjects. The mean plasma cholesterol level during the trial period was 6.91, 6.16, and 5.54 mmol per liter, respectively (267, 238, and 214 mg per dl), in controls, diet-treated, and diet-plus-drug-treated subjects.

The proportion of subjects who showed overall progression of coronary artery narrowing (reduced average diameter of coronary artery segments) was significantly smaller in both interventions groups: 15% in the diet group, 12% in the diet plus cholestyramine group, and 46% in the usual-care group. The proportion who showed an increase in average coronary artery segment diameters was 38%, 33%, and 4% respectively, in these groups. The mean absolute width of coronary artery segments decreased by 0.201 mm in the usual-care group, increased by 0.003 mm in diet-treated, and increased by 0.103 mm in diet-plus-cholestyramine-treated subjects ($P < .05$). Changes in coronary artery segmental diameter were independently and significantly correlated with the LDL-cholesterol concentration and the ratio of LDL- to HDL-cholesterol during the trial period. Both interventions reduced the frequency of total cardiovascular events in subjects who did not drop out of the trial.

Several computer-derived end points were also measured, including the percentage of diameter stenosed as used in other trials, minimum segment-width segments, and an index of vessel edge irregularity. It is of considerable interest that the diameter of stenosis showed significant evidence for regression from both treatments in lesions that were greater than 50% stenosed at baseline ($P = .05$) but not in lesions that were 15% to 50% stenosed at baseline ($P = .27$). Both treatments significantly reduced progression in lesions less than 15% stenosed at baseline ($P = .04$).

This study adds to the evidence that dietary change alone that reduces blood total cholesterol levels 15% can retard overall progression and increase the overall regression of coronary artery disease. When diet was augmented by the use of cholestyramine, the reduction in blood cholesterol levels was 24% and coronary benefits were increased. Another important feature is the comparison of lesion response according to baseline severity. This trial confirms the differential treatment effects seen when visible lesions (greater than 15% stenosed) are stratified above and below the level of 50% stenosis. It takes advantage of the increased sensitivity possible with fully automated edge finding to provide information on lesions of less than 15% stenosis. This class of lesions has not received attention because the human panel reading methods used in the NHLBI Type II Study, the Cholesterol Lowering Atherosclerosis Study, and the Program on the Surgical Control of the Hyperlipidemias do not detect them. The same limitation applies to the quantitative procedure used in the Familial Atherosclerosis Treatment Study and the University of California, San Francisco, trials, which depends on humans to trace vessel edges for digitization by a light pen. The Life-style Heart Trial used a method that could have detected changes in these lesions but did not report them. Fully automated computerized evaluations of CLAS films and of the trial of the use of lovastatin (Monitored Atherosclerosis Regression Study)[23] also indicate the substantial effects of baseline lesion status on treatment results.

Conclusions

Together the findings of the controlled clinical trials reviewed here provide convincing evidence that it is possible to reduce the progression and to induce the regression of human atherosclerosis.* Furthermore, from the limited available data, women appear to be more responsive to antiatherosclerosis treatment than men. The degree of change observed in any single lesion with lipid lowering is small compared with what can be accomplished with angioplasty, and there is no selectivity in which lesions will change. The trials have used several different procedures to evaluate coronary artery change, which adds to the overall strength of evidence that atherosclerosis can be modified, but reduces the ability to evaluate the consistency of change across studies. Despite these differences, a theme that emerges from all trials that have made comparisons (the NHLBI Type II, the Familial Atherosclerosis Treatment Study, Life-style Heart Trial, the St Thomas' Atherosclerosis Regression Study, the Monitored Atherosclerosis Regression Study, and CLAS [unpublished]) is that the response to therapy is substantially influenced by the status of lesions at baseline. What is surprising is that the greatest treatment benefits have been in the most severe lesions, those of more than 50% in diameter stenosis at baseline.

A challenge for the future is to reconcile these angiographic trial findings with what we know of the histopathology of atherosclerosis—that is, large lesions have more complicated features than small lesions. Because angiographic trials do not provide information on events within the arterial wall at the level of cell function and deal only with lesions that intrude into the vessel lumen, other methods to track a change in lesions will probably also be needed. As a first step, imaging procedures should be developed that can provide more frequent measurements of plaque status. A second necessary step, until the serial assessment of arterial cell function is possible, will be to correlate serial imaging in animal models with disease structure. This could be done by adding one of several current noninvasive evaluations of wall status, such as magnetic resonance imaging, ultrafast computed tomography, and ultrasound imaging, to animal model experiments. Among these, the least expensive would be ultrasound imaging. None of these procedures would interfere with the traditional practices in animal model atherosclerosis research, such as the killing of test and control animals for histopathologic and cell system studies.

Current theories of atherogenesis suggest a number of targets for intervention to retard lesion progression and foster regression. Two trials not included in this review that tested calcium channel blockade indicate that new coronary artery lesions can be prevented by therapies that may not cause the reversal of early lesions.[24,25] These re-

*See also the editorial by B. G. Brown, MD, "Regression of Atherosclerosis—An Ounce of Prevention," on pages 208-210.

sults, plus growing evidence that relatively early intrusive lesions can be dangerous,[26,27] indicates the need to expand the knowledge of atherosclerosis treatment effects to all stages of the disease. From what we now know of the disease, control through the suppression of early stages of early lesions appears more likely to be feasible than completely preventing the atherosclerotic process.

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